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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,177	COME ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63 and 65* is/are pending in the application.

4a) Of the above claim(s) *1-27,47,56-62 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-46,48-55 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 8/24/2006, in which claims 64 and 66 were canceled; and claims 38, 42 and 48 were amended. Currently, claims 1-63 and 65 are pending.

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 1/6/2006. Therefore, this action is not final.

Election/Restrictions

Applicant elected Group IV with traverse in the reply filed on 7/20/2005.

Applicant elected the following species: "methotrexate or a derivative thereof" for R1, and "identifying a positive ligand binding cell in which an increase in the level of transcription of the reporter gene has occurred for the method step of detecting (see pages 21-22 of the response filed 7/20/2005).

Claims 1-27, 47, 56-62 and 65 are withdrawn from consideration as being drawn to a non-elected invention. Applicant timely traversed the restriction (election) requirement in the replies filed on 7/20/2005 and 10/3/2005.

The species election requirements for elected Group IV have been WITHDRAWN. Claims 32 and 43-45 have been rejoined.

Claims 28-46, 48-55 and 63 read on the elected invention and are under consideration.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: reference numbers 1-41 of Figures 1A-F are not separately described in the "Brief Description of the Figures" section of the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 42 is objected to because of the following informalities: the claim recites "FK506" and "FK506 derivative" in line 3; however, the last three lines of the claim provide for derivatives of the recited structures. Thus, it is redundant to recite both ""FK506" and "FK506 derivative" in line 3. It would be remedial to amend the claim to delete "FK506 derivative." Appropriate correction is required. This is a new objection.

Response to Arguments - Claim Objections

The objection of claims 64 and 66 is moot in view of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 45 is vague and indefinite in that the metes and bounds of the phrase "involves the use of a cell providing an N-end rule degradation system" are unclear. The claim does not provide the relationship between the cell with the N-end rule degradation system and the method steps of the three-hybrid assay of claim 43 or 44. Thus, it is unclear how the cell is used in the assay. It would be remedial to amend the claim language to clearly indicate that claim 45 is drawn to the method of claim 43 or 44, wherein said first ligand-binding polypeptide and said second ligand-binding polypeptide are provided in a cell with an N-end rule degradation system.

Response to Arguments - 35 USC § 112

Applicant's arguments, see pages 24-25, filed 5/24/2006, with respect to the rejection of claims 38-42 and 48-49 under 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive. The previous rejection of claims 38-42 and 48-49 has been withdrawn.

Applicant's arguments, see page 25, filed 5/24/2006, with respect to the rejection of claims 38-42 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, have been fully considered and are persuasive. The previous rejection of claims 38-42 has been withdrawn.

Applicant's arguments, see pages 25-26, filed 5/24/2006, with respect to the rejection of claims 28-31, 33-42, 46, 48-55 and 63 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, have been fully considered and are persuasive. The previous rejection of claims 28-31, 33-42, 46, 48-55 and 63 has been withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28, 30-31, 33-34 and 52-53 are rejected under 35 U.S.C. 102(b) as being unpatentable over Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998; see the entire reference) as evidenced by Amara et al (PNAS, USA, Vol. 94, pages 10618-10623, 1997;

see the entire reference) and Bierer et al (PNAS, USA, Vol. 87, pages 9231-9235, 1990; see the entire reference).

Regarding claims 28 and 33-34, Keenan et al teach the method to identify binding of a polypeptide sequence to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand such as dimerized FK1012 linked by polyehtylene linkers, (ii) introducing the hybrid ligand into a population of cells containing a SEAP reporter gene operably linked to ZFHD1 binding sequences, a first chimeric gene encoding a fusion protein containing three FKBP binding domains and a DNA binding domain from ZFHD1, and a second chimeric gene encoding a fusion polypeptide containing three FKBP binding domains and a transcription activation domain from the NF-κB p65 subunit, and (iii) allowing the hybrid ligand to bind the FKBP binding domains to induce dimerization such that transcription of the SEAP reporter gene is increased, and (iv) identifying positive ligand binding cells by activation of SEAP, and (v) identifying the nucleic acid sequence of the second chimeric gene (e.g. page 1334, Assay for inducible transcriptional activation; Figure 3; Table 1). Keenan et al teach that the method used to assay for inducible transcriptional activation was performed as previously described by Amara et al (e.g. page 10620, right column, 1st full paragraph; paragraph bridging pages 10618-10619; Figure 4). Keenan et al teach the use of hybrid ligands, wherein R1 and R2 are FK1012 and Y is of the formula $(CH2\text{-}O\text{-}CH2)_n$, where n=2, 3, 4 or 5, (e.g. Table 1, compounds AP1427, AP1592, AP1511, and AP1578).

Regarding claims 30-31, the hybrid ligands taught by Keenan et al bind to FKBP with a dissociation constant (K_D) of less than 1 μM. Keenan et al teach that the affinity of structure 2d is threefold better than the original model monomer 2a, and the prior art teaches that the

dissociation constant of FK506 to FKBP is in the nanomolar range (e.g. Bierer et al, page 9231, paragraph bridging columns). Bierer et al is used here only to demonstrate that the dissociation constants of the ligands taught by Keenan are less than 1 μM.

Regarding claim 52, Keenan et al teach the addition of the hybrid ligand to cells in the absence of the fusion proteins (e.g. Table 1, Apoptosis; page 1334, Assay for inducible Fas activation in cell lines).

Regarding claim 53, Keenan et al teach the measurement of SEAP activity in mock transfected cells to identify background SEAP activity in the absence of the hybrid ligand (e.g. page 1334, Assay for inducible transcriptional activation).

Response to Arguments - 35 USC § 102

Applicant's arguments, see page 26, filed 5/24/2006, with respect to the rejection of claims 38, 42, 52-53 and 63 under 35 U.S.C. 102(a) as being anticipated by Lin et al have been fully considered and are persuasive. The previous rejection of claims 38, 42, 52-53 and 63 has been withdrawn. This rejection was made in the Office action mailed 1/6/2006 and is reiterated below.

Applicant's arguments, see page 27, filed 5/24/2006, with respect to the rejection of claims 46 and 63 under 35 U.S.C. 102(b) as being unpatentable over Keenan et al, as evidenced by Amara et al and Bierer et al, have been fully considered and are persuasive. The previous rejection of claims 46 and 63 has been withdrawn.

With respect to the rejection of claims 28, 30-31, 33-34 and 52-53 under 35 U.S.C. 102(b) as being unpatentable over Keenan et al, as evidenced by Amara et al and Bierer et al, Applicant's arguments filed 5/24/2006 have been fully considered but they are not persuasive.

The response asserts that Keenan fails to teach a screening method to identify a polypeptide that binds to a user specified ligand, never teaches or suggests that R1 and R2 can be different, and does not teach or suggest any screening assay in which a library of candidate binding proteins are to be expressed in cells, so that those candidate binding proteins that actually bind one of the two monomers on the ligand R2 can be identified. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., library of candidate binding proteins and a ligand where R1 is different from R2) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Keenan et al test hybrid ligands that meet the structural limitations of the claims in the three-hybrid assay to identify whether the DNA binding domain and activation domain fusion proteins are capable of binding.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 54-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keenan et al (Bioorg. Med. Chem. Vol. 6, pages 1309-1335, 1998; see the entire reference) as evidenced by Amara et al (PNAS, USA, Vol. 94, pages 10618-10623, 1997; see the entire reference) in view of Mehta (WO 00/07018; see the entire reference). This rejection was made in the Office action mailed 1/6/2006 and is reiterated below.

The teachings of Keenan et al are described above and applied as before.

Keenan et al do not teach the use of a microtiter plate to confirm that the transcription of the reporter gene is dependent on the presence of the hybrid ligand.

Mehta et al teach the confirmation of the dependence of yeast three hybrid ligand interactions on the presence of both fusion proteins and the hybrid ligand by placing yeast cells in a well of a 96 well plate with hybrid ligand only or no hybrid molecule to serve as controls in the assay (e.g. Example 4). Further, Mehta et al teach the screening of libraries to identify

numerous proteins that may interact with the hybrid ligand and teach the confirmation of the interactions using the 96-well microtiter assay (e.g. Example 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the yeast three hybrid assay of Keenan et al to include the use of the mcirotiter plate as taught by Mehta et al because both Keenan et al and Mehta et al teach it is within the ordinary skill in the art to use hybrid ligands in a yeast three hybrid assay. Further, it would have been obvious to conduct the assay on greater than 10 ligand-binding cell types because the assay can result in the identification of at least 10 ligand-binding cell types or can be repeated at least 10 times to identify 10 ligand-binding cell types.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to use fewer reagents and to be able to perform more assays in less space by using the microtiter plate as taught by Mehta et al. Further, one would have been motivated to conduct the assay on at least 10 ligand-binding cell types in order to confirm each interaction identified in the screen. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsson et al (US Patent No. 5,585,245, cited as reference P04 on the IDS filed 4/26/2003; see the entire reference) in view of Licitra et al (PNAS, USA, Vol. 93, pages 12817-12821, 1996, cited in a prior action; see the entire reference), as evidenced by Varshavsky et al (PNAS, USA, Vol. 93, pages 12142-12149, 1996; see the entire reference).

Johnsson et al teach a method of identifying the binding between a predetermined member of a specific-binding pair and a previously unidentified member of the specific-binding pair, comprising the steps of (i) providing a first DNA-based expression vector containing an expression cassette encoding a C-terminal subdomain of ubiquitin fused in frame to DNA encoding P1 and to a reporter moiety if P1 does not double as a reporter, (ii) providing a second DNA-based expression vector containing an expression cassette encoding randomly generated genomic or cDNA fragments fused to DNA (P2) encoding the N-terminal subdomain of ubiquitin (Nux), (iii) co-transforming a eukaryotic host cell with the first and second vectors such that the fusion proteins are produced, (iv) detecting cleavage of the fusion protein by the reconstituted ubiquitin moiety (e.g. column 9, lines 28-39; column 12, line 12 to column 13, line 20). Further, Johnsson et al teach that the C-terminal subdomain must bear an amino acid extension (i.e., to form Cub-Z) (e.g. column 6, lines 24-26). Thus, the first expressed fusion protein comprises segments P1, Cub-Z and RM, in an order where Cub-Z is closer to the N-terminus than RM (e.g. column 6, lines 24-26; column 12, line 12 to column 13, line 20; Figure 1D). Johnsson et al teach that the arrangement can also be reversed to have the randomly generated fragment fused to the C-terminal ubiquitin subdomain rather than the N-terminal subdomain (e.g. column 13, lines 15-20). Johnsson et al teach that the system may be used with transmembrane proteins (e.g. column 20, lines 34-45).

Varshavsky is cited only to show that N-end rule degradation operates in all organisms examined, from mammals to fungi and bacteria (e.g. Abstract; page 12147, left column, 1st full paragraph). Thus, the eukaryotic cells taught by Johnsson et al have an N-end rule degradation system.

Johnsson et al do not teach the step of providing a hybrid ligand represented by the general formula R1-Y-R2, wherein R1 is different from R2, at least one of R1 and R2 is not a peptide, Y is a linker, and R2 binds the second ligand-binding polypeptide at P2.

Licitra et al teach a yeast three-hybrid assay, wherein a hybrid ligand of Dexamethasone and FK506 is used to screen a cDNA library for proteins capable of binding to FK506 (e.g. page 12818, Three-Hybrid Screen for FK506-Binding Proteins; Figures 1-3). A first hybrid protein comprising a DNA-binding domain and receptor for Dexamethasone (P1) was provided, and a second hybrid ligand comprising a potential receptor for FK506 (P2) and a transactivation domain was provided (e.g. Figures 2-4). Licitra et al teach the identification of positive interactions using the LacZ reporter gene (e.g. Figure 3). Licitra et al teach that the yeast three-hybrid assay has advantages over classical methods for identifying receptors for small ligand in that the system allows the direct isolation and identification of cDNAs encoding receptors and the system easily allows one to manipulate a large number of yeast colonies to study the structure-function relationship of ligand receptor interaction (e.g. page 12820, right column, last full paragraph). Further, Licitra et al suggest the use of other two- and three-hybrid systems that would allow the utility of the system to be expanded to other types of proteins such as membrane proteins (e.g. page 12820, right column, 1st full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the two-hybrid method of Johnsson et al to include the hybrid ligand, P1 and P2 portions taught by Licitra et al because Licitra suggest the use of other two- or three-hybrid systems to expand the utility of the assay comprising the hybrid ligand and Johnsson et al teaches a version of a two-hybrid method.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to identify membrane proteins capable of interacting with FK506 as suggested by Licitra and as taught by Johnsson et al. This modification would expand the utility of the hybrid ligand screening assay. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46, 48-50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference). This is a new rejection.

Liu et al teach a screening assay for identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand having the general formula A-L-B (or R1-L-R2), where A is a first ligand and B is a user-specified ligand different from A, (ii) introducing the hybrid ligand into a sample containing a functional transcriptional and translational apparatus (for example, a whole cell) that includes vectors a encoding a hybrid protein including a transcription module and a target module for binding ligand A (P1) or for binding ligand B (P2) (target proteins #1 and #2), (iii) once the three hybrid complex comprising the hybrid ligand, first fusion protein and second fusion protein is formed, transcriptional activation of a reporter gene occurs, and (iv) retrieving the plasmid encoding the fusion protein capable of binding to B and sequencing the plasmid (e.g. column 5. line 55 to column 8, line 46; column 11, lines 25-32; Figure 2). Liu et al teach that one of the vectors capable of binding the

ligand contains a DNA binding domain and the other contains a transcription activation domain (e.g. column 7, lines 24-59; Figures 1-3). Liu et al teach that the nucleic acid sequence encoding the ligand B binding domain polypeptide is from random DNA sequences of a size that is capable of encoding a yet undetermined target protein, where the random sequences are derived from a genomic DNA library, cDNA library or synthetically generated library formed from eukaryotic cells, prokaryotic cells, viruses, or formed by an automated DNA synthesizer (e.g. paragraph bridging columns 7-8). With regard to the affinity of the hybrid ligand A to P1, Liu et al teach binding affinities including a Kd below 10^{-6}, 10^{-7}, 10^{-8} or 10^{-9} (e.g. column 8, lines 31-46). Liu et al teach that ligand A may be selected based upon a strong binding affinity for a target encoded by a fusion gene; the binding affinity must necessarily be measured if this determination is made (e.g. column 8, lines 31-46). Liu et al teach that A may form a covalent bond with P1 if a suicide inhibitor is used, for example beta-lactamase as P1 can covalently bind suicide inhibitors used as ligand A, including beta-lactam antibiotics (e.g. paragraph bridging columns 5-6). With regard to the reporter gene, Liu et al teach the use of LacZ, and GFP (e.g. column 8, lines 17-30; Figures 1-3). With regard to ligand B, Liu et al teach that the ligand may be selected from FK506, peptide libraries, nucleic acid libraries, polysaccharide libraries, and small organic molecules (e.g. column 6, lines 14-26). Liu et al teach the use of control experiments containing hybrid ligand only (without target proteins #1 and #2) to determine if the effects of the hybrid ligand are independent of trimeric complex formation (e.g. Example 5). Liu et al teach the use of control experiments to confirm that reporter gene activation does not occur in the presence of the two target proteins in the absence of the hybrid ligand (e.g. column 11,

lines 11-32). Liu et al teach that ligand A and ligand B may be covalently linked by any of the methods known in the art (e.g. column 6, lines 27-37).

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the

ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-36, 46, 48-50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference) and Lin et al (Journal of the American Chemical Society, Vol. 122, pages 4247-4248 and supporting pages S1-S12, published online 4/13/2000, cited in a prior action; see the entire reference). This is a new rejection.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the three-hybrid method where A (or R1) is methotrexate.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Lin et al teach a method of identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand comprising methotrexate linked to dexamethasone through a linker region, (ii) introducing the hybrid ligand into yeast cells comprising a LacZ reporter gene operably linked to a LexA binding site, a first chimeric gene encoding a fusion polypeptide of LexA and DHFR, a second chimeric gene encoding a fusion protein of GR and B42, (iii) allowing the hybrid ligand to bind the first and second fusion proteins to result in an increase in the level of the transcription of the reporter gene, (iv) identifying a positive ligand binding cell by detecting blue colonies of yeast grown on X-gal containing plates, and (v) identifying the nucleic acid sequence of the second chimeric gene (e.g. page 4248, left column; Figures 1 and 2; Scheme 1; page S6). Further, Lin et al teach the assay where one of the fusion proteins is deleted to detect the effect of the hybrid ligand independent

of the formation of the trimeric complex of the two fusion proteins and the hybrid ligand (e.g. page 4248, left column, last paragraph). Moreover, Lin et al teach the assay in the absence of the hybrid ligand to confirm that the transcription of the reporter gene is dependent on the presence of the hybrid ligand and fusion proteins (e.g. Figure 2). Lin et al teach that methotrexate can be modified readily without disrupting receptor binding, is commercially available, and has a picomolar affinity for DHFR (e.g. page 4247, right column, 1st paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious at the time the invention was made to modify the hybrid ligand of Liu et al to include methotrexate as A (or R1), because Liu et al teach that A can be varied and Lin et al teach the use of methotrexate in a three-hybrid assay.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Further, one would have been motivated to use methotrexate as R1, because Lin et al teach that methotrexate can be modified readily without disrupting receptor binding, is commercially available, and has a picomolar affinity for DHFR. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference) and Karlsson et al (US Patent No. 6,143,574, cited in a prior action; see the entire reference). This is a new rejection.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the use of plasmon resonance to determine the binding affinity of A to a fusion protein.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page

4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Karlsson et al teach that the BIAcore instrument uses the phenomenon of surface plasmon resonance to study the binding of analytes to receptors immobilized on a sensor chip to allow the affinity and kinetic analysis of interactions between soluble analytes and their immobilized binding partners to be determined (e.g. column 1, lines 11-45). Karlsson et al teach that affinity and kinetic properties for the solution interaction between an analyte and a binding partner can be determined by the following steps: (i) mixing the analyte with an immobilized binding partner (e.g. column 2, lines 3-15; column 3, lines 17-20). Karlsson et al teach that the method provides the ability to not only determine the true affinity properties but also true kinetic properties for the solution interaction between an analyte and binding partner therefore to thereby among other things be permitted a wider choice of reaction partners than in solid phase interactions and avoid immobilization artifacts (e.g. column 1, lines 59-65).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious at the time the invention was made to include the use of plasmon resonance to determine the binding affinity of A to P1, because Liu et al teach it is within the skill of the art to select A and P1 based upon binding affinity and Karlsson et al teach a method of determining binding affinity using plasmon resonance.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Further, one would have been motivated to use the plasmon resonance method of Karlsson et al in order to receive the expected benefit of providing the ability to not only determine the true affinity properties but also true kinetic properties for the solution interaction between an analyte and binding partner therefore to thereby among other things be permitted a wider choice of reaction partners than in solid phase interactions and avoid immobilization artifacts. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46, 48-50, 52, 53 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference) and Licitra et al (PNAS, USA, Vol. 93, pages 12817-12821, 1996, cited in a prior action; see the entire reference). This is a new rejection.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the step of providing access to data, nucleic acids or peptides obtained from the identification of polypeptide binding to a hybrid ligand.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Licitra et al teach a yeast three-hybrid assay, wherein a hybrid ligand of Dexamethasone and FK506 is used to screen a cDNA library for proteins capable of binding to FK506 (e.g. page 12818, Three-Hybrid Screen for FK506-Binding Proteins; Figures 1-3). Licitra et al teach the identification of positive interactions using the LacZ reporter gene and disclose the data in the publication (e.g. Figure 3). Licitra et al teach that the yeast three-hybrid assay has advantages over classical methods for identifying receptors for small ligand in that the system allows the direct isolation and identification of cDNAs encoding receptors and the system easily allows one to manipulate a large number of yeast colonies to study the structure-function relationship of ligand receptor interaction (e.g. page 12820, right column, last full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious to provide the public access to the data through publication as taught by Licitra et al, because Liu et al teach a three-hybrid assay and Licitra teach a three-hybrid assay and provide the data obtained from the assay.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. One would have been motivated to publish the data obtained from such an assay to be able to communicate the findings to peers in the form of a publication. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36-42, 46, 48-50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868; see the entire reference) in view of Bertozzi et al (J. Org. Chem., Vol. 56, pages 4326-4329, 1991, cited as reference CC on the IDS filed 7/20/2005; see the entire reference) and Zaharevitz et al (Cancer Research, Vol. 59, pages 2566-2569, 1999; see the entire reference). This is a new rejection.

The teachings of Liu et al are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5. Liu et al do not teach the method where ligand B is a cyclin dependent kinase inhibitor of Table 2.

At page 4326, Bertozzi et al teach a linker of the following formula:

Bertozzi et al teach that polyethylene glycol derivatives are ideal for the purpose of linking two compounds to make bifunctional molecules for the study of enzymes and receptors, because they are inexpensive, water soluble, and available in a variety of lengths (e.g. page 4326, paragraph bridging column). Bertozzi et al teach that the heterobifunctional linker of the above structure contains a free amine that can be conjugated to biological molecules directly by an amide linkage (or via the corresponding isothiocyanate) and an azide that can be reduced to an amine for conjugation to other molecules (e.g. page 4326, right column). The free amine and azide of the structure of Bertozzi et al is an improvement of the prior art structures, because the Bertozzi structure is easier to link to biomolecules for the formation of bifunctional compounds (e.g. page 4326). Bertozzi et al exemplify a hybrid ligand comprising mannose linked to fluoescein with a $(CH_2\text{-}O\text{-}CH_2)_3$ linker (e.g. page 4327, left column).

Zaharevitz et al teach a small molecule cyclin dependent kinase inhibitor found on page 1 of instant Table 2 (e.g. Figures 1 and 4). Zaharevitz et al teach that these compounds are novel and are able to interact with a subset of CDKs (e.g. paragraph bridging pages 2568-2569). Further, Zaharevitz et al teach that the disclosed compounds are useful as a tool for exploring the structural bases and pharmacological significance of various kinase specificites.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the linker comprising a free amine and azide of Bertozzi et al because Liu et al teach it is within the ordinary skill in the art to use any method known in the art to link ligands A and B to form a hybrid molecule and Bertozzi et al teach the use of the linker to form a hybrid ligand. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the CDK inhibitors disclosed by Zaharevitz et al as ligand B, because Liu et al teach that ligand B may be selected from a small molecule library and Zaharevitz et al teach that the kinase inhibitor is a small molecule.

One would have been motivated to make such a modification in order to receive the expected benefit of easily linking ligands A and B as taught by Bertozzi et al. Further, one would have been motivated to use the kinase inhibitors of Zaharevitz et al as ligand B to be able to screen for other kinases capable of binding the inhibitors to further characterize the kinase specificities of the inhibitors. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 38-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868; see the entire reference) in view of Zaharevitz et al (Cancer Research, Vol. 59, pages 2566-2569, 1999; see the entire reference). This is a new rejection.

Liu et al teach a screening assay for identifying a polypeptide sequence that binds to a user-specified ligand, comprising the steps of (i) providing a hybrid ligand having the general formula A-L-B (or R1-L-R2), where A is a first ligand and B is a user-specified ligand different from A, (ii) introducing the hybrid ligand into a sample containing a functional transcriptional and translational apparatus (for example, a whole cell) that includes vectors a encoding a hybrid protein including a transcription module and a target module for binding ligand A (P1) or for binding ligand B (P2) (target proteins #1 and #2), (iii) once the three hybrid complex comprising the hybrid ligand, first fusion protein and second fusion protein is formed, transcriptional activation of a reporter gene occurs, and (iv) retrieving the plasmid encoding the fusion protein capable of binding to B and sequencing the plasmid (e.g. column 5. line 55 to column 8, line 46; column 11, lines 25-32; Figure 2). Liu et al teach that one of the vectors capable of binding the ligand contains a DNA binding domain and the other contains a transcription activation domain (e.g. column 7, lines 24-59; Figures 1-3). Liu et al teach that the nucleic acid sequence encoding the ligand B binding domain polypeptide is from random DNA sequences of a size that is capable of encoding a yet undetermined target protein, where the random sequences are derived from a genomic DNA library, cDNA library or synthetically generated library formed from eukaryotic cells, prokaryotic cells, viruses, or formed by an automated DNA synthesizer (e.g. paragraph bridging columns 7-8). With regard to the affinity of the hybrid ligand A to P1, Liu et al teach binding affinities including a Kd below 10^{-6}, 10^{-7}, 10^{-8} or 10^{-9} (e.g. column 8, lines 31-46). Liu et al teach that ligand A may be selected based upon a strong binding affinity for a target encoded by a fusion gene; the binding affinity must necessarily be measured if this determination is made (e.g. column 8, lines 31-46). Liu et al teach that A may form a covalent

bond with P1 if a suicide inhibitor is used, for example beta-lactamase as P1 can covalently bind suicide inhibitors used as ligand A, including beta-lactam antibiotics (e.g. paragraph bridging columns 5-6). With regard to the reporter gene, Liu et al teach the use of LacZ, and GFP (e.g. column 8, lines 17-30; Figures 1-3). With regard to ligand B, Liu et al teach that the ligand may be selected from FK506, peptide libraries, nucleic acid libraries, polysaccharide libraries, and small organic molecules (e.g. column 6, lines 14-26). Liu et al teach the use of control experiments containing hybrid ligand only (without target proteins #1 and #2) to determine if the effects of the hybrid ligand are independent of trimeric complex formation (e.g. Example 5). Liu et al teach the use of control experiments to confirm that reporter gene activation does not occur in the presence of the two target proteins in the absence of the hybrid ligand (e.g. column 11, lines 11-32). Liu et al teach that ligand A and ligand B may be covalently linked by any of the methods known in the art (e.g. column 6, lines 27-37).

Liu et al do not teach the method where ligand B is a cyclin dependent kinase inhibitor of Table 2.

Zaharevitz et al teach a small molecule cyclin dependent kinase inhibitor found on page 1 of instant Table 2 (e.g. Figures 1 and 4). Zaharevitz et al teach that these compounds are novel and are able to interact with a subset of CDKs (e.g. paragraph bridging pages 2568-2569). Further, Zaharevitz et al teach that the disclosed compounds are useful as a tool for exploring the structural bases and pharmacological significance of various kinase specificites.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand of the three-hybrid method of Liu et al to include the CDK inhibitors disclosed by Zaharevitz et al as ligand B, because Liu et al teach that ligand B may be

selected from a small molecule library and Zaharevitz et al teach that the kinase inhibitor is a small molecule.

One would have been motivated use the kinase inhibitors of Zaharevitz et al as ligand B to be able to screen for other kinases capable of binding the inhibitors to further characterize the kinase specificities of the inhibitors. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 28-34, 36, 46, 48-50, 52, 53 rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent No. 5,928,868; see the entire reference) in view of Holt et al (WO 96/06097, cited as reference AD on the IDS filed 4/28/2003; see the entire reference). This is a new rejection.

The teachings of Liu are described above and applied as before.

Liu et al do not teach the linker between ligand A (or R1) and B (or R2) with the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 2-5.

Holt et al teach the formation of heterodimers of immunophilin ligand moieties (e.g. FK506 and derivatives thereof) (e.g. page 1; page 6, lines 12-17). Holt et al exemplify structures linked by polyethylene linkers of the formula $(CH_2\text{-}O\text{-}CH_2)_n$, where n = 1, 2, 3, 4 (e.g. pages 14-15). Holt et al teach the use of the homodimeric ligands comprising the abovementioned linker where n = 2 or 3 in an cell-based transfection assay where a trimeric complex comprising the homodimeric ligand, a fusion protein comprising three copies of FKBP12 fused to a Gal4 DNA binding domain, and a fusion protein comprising three copies of FKBP12 fused to a VP16

activation domain was detected by the production of the reporter product, secreted alkaline phosphatase (e.g. pages 48-49). Holt et al teach that multimerizers vary somewhat in their observed activity, depending upon the particular chimeric proteins and other components of the system and recommend that the practitioner select multimerizers based upon their performance in the particular system of interest (e.g. page 48 lines 26-30).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the hybrid ligand in the three-hybrid assay to include the $(CH_2\text{-}O\text{-}CH_2)_n$ linker of Holt et al because Liu et al teach it is within the ordinary skill in the art to use any linker known in the art and Holt et al teach linkers for making homodimeric or heterodimeric ligands capable of forming a trimeric complex in three hybrid assay.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to vary the linker of the hybrid ligand to determine which ligand performs best in the three-hybrid system as taught by Holt et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicant's arguments, see pages 28-29, filed 5/24/2006, with respect to the rejection of claims 29 and 36 under 35 U.S.C. 103(a) as being unpatentable over Keenan et al in view of Licitra et al, as evidenced by Amara et al, have been fully considered and are persuasive. The previous rejection of claims 29 and 36 has been withdrawn.

Applicant's arguments, see pages 28-29, filed 5/24/2006, with respect to the rejection of claims 29, 35-36, 41 and 48-50 under 35 U.S.C. 103(a) as being unpatentable over Keenan et al in view of Licitra et al further in view of Lin et al, as evidenced by Amara et al, have been fully considered and are persuasive. The previous rejection of claims 29, 35-36, 41 and 48-50 has been withdrawn.

Applicant's arguments, see pages 28-29, filed 5/24/2006, with respect to the rejection of claims 29, 35-36, 41 and 48-51 under 35 U.S.C. 103(a) as being unpatentable over Keenan et al in view of Licitra et al further in view of Lin et al, Sota et al and Karlsson et al, as evidenced by Amara et al, have been fully considered and are persuasive. The previous rejection of claims 29, 35-36, 41 and 48-51 has been withdrawn.

Applicant's arguments, see page 30, filed 5/24/2006, with respect to the rejection of claims 54-55 under 35 U.S.C. 103(a) as being anticipated by Lin et al in view of Mehta have been fully considered and are persuasive. The previous rejection of claims 54-55 has been withdrawn.

With respect to the rejection of claims 54-55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Keenan et al, as evidenced by Amara et al, in view of Mehta, Applicant's arguments filed 5/24/2006 have been fully considered but they are not persuasive.

The response asserts that the rejection was made on the assumption that R1 (methotrexate) is a kinase inhibitor. This is not found persuasive, because claims 54 and 55 depend from claim 28, which does not require R1 or R2 to be a kinase inhibitor.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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CELINE QIAN, PH.D.
PRIMARY EXAMINER